HIGH SPEED MULTIPLE ECHO ACQUISITION (HISTO): A RAPID AND SIMULTANEOUS ASSESSMENT OF FAT AND IRON CONTENT IN LIVER BY ^{1}HMRS, VALIDATION ON PHANTOMS AND PATIENTS.

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ABSTRACT

Proton MR Spectroscopy (^{1}H MRS) offers a means for noninvasively determining hepatic lipids (HL) and provides acceptable spectral resolution and high sensitivity even with low amounts of HL. ^{1}H-MRS is also used to accurately quantify the iron overload in the liver. In this work, we introduce a technique that allows the rapid, accurate and simultaneous assessment of fat and iron content which could be applied for single breath hold liver MRS. The feasibility and accuracy of this technique has been demonstrated experimentally in phantoms and applied to patients with fatty liver disease.

Index Terms—MRS, liver, steatosis, iron, T2, lipids

1. INTRODUCTION

Obesity related fatty liver disease has become the most common cause of hepatitis and fibrosis in the developed nations, affecting young adults and children. Detection and monitoring of disease currently depend upon invasive biopsies. Liver biopsies may be painful and may cause bleeding, potentially leading to serious complications and even death in 1% of patients. Various MRI techniques have been introduced for the detection or visualization of fat in the liver. Proton MR Spectroscopy (^{1}H-MRS) offers a means for noninvasively determining hepatic lipids (HL) and provides acceptable spectral resolution and high sensitivity even with low amounts of HL. Furthermore, liver iron concentration is considered another important factor that may contribute to hepatitis and cirrhosis. Many studies have demonstrated strong correlation between R2 (1/T2, T2 being the transverse relaxation time) and liver iron content in MRI. Two of them have specifically compared the amount of iron measured at liver biopsy to MRI measurements of R2 and R2*, identifying a strong correlation between R2 and hepatic iron concentration with acceptable inter-exam reproducibility [1,2]. MRS has been used to assess T2 values of water signal, using single voxel STEAM sequences at a number of echo times (TE) and fitting an exponential decay to the echo amplitude at different TEs [3]. One major difficulty of relaxation time-based MRI studies is represented by low signal intensities from the tissue of interest under heavy iron load because of shortened T2. Another limitation of prior reports is the use of relatively long acquisition times, generally requiring multiple acquisitions of spectra and complicated correction schemes. In this work, we introduce a technique applicable to single breath hold liver MRS that allows the rapid and simultaneous assessment of fat content and iron content. It consists of a concatenation of multiple repeats of a basic sequence (STEAM or PRESS), where each repeat has a different TE. The acquisition of multiple echoes allows calculating the T2 and S_0 values of water and fat; having the S_0 values of both signals, we were able to assess the T2 corrected lipid content.

2. MATERIALS AND METHODS:

2.1. Phantoms

We created twelve 200 mL phantoms. “Tissue water” space was simulated with 2% agar-water gels with varying concentrations of iron (Feridex, Berlex, NJ) (0, 0.1, 0.3, 0.5 mM) and varying percentage of fat, a vegetable oil (0, 10 and 30% per volume) at a pH of 7.00 +/- 0.2. The mixture was contained within 200mL screw-top tubes. Micelles were produced by the addition of lecithin at a concentration of 2% wt/vol.

2.2. Subjects

The study protocol was reviewed and approved by our institution’s Internal Review Board. Two patients diagnosed with fatty liver disease were investigated in this study.

2.3 MRS

A new sequence named HISTO for high speed multiple echo acquisition was developed. The method is a

concatenation of multiple repeats of a basic sequence (STEAM or PRESS) aimed at obtaining data from a selected region with different TEs. The first TE is the shortest one, and after a constant time period (repetition time (TR)) the basic sequence is reapplied multiple times with different parameters for acquiring the remaining TEs (figure 1). On a 1.5 Tesla MRI system (Avanto, Siemens Medical Solutions, Malvern, PA) with a surface coil, after scout imaging, water spectra of phantoms were obtained with HISTO, based on the STEAM pattern, using a TR of 3 sec, TM = 10 ms and five TEs (12, 24, 36, 48 and 72 ms). For the high iron concentration phantoms, we applied TEs of 12, 15, 18, 21 and 24 ms. The bandwidth was 1200 Hz and 1024 points were acquired with one signal accumulation. The voxel size was 30x30x30 mm^3. For the MRS in the patients, the voxel was placed in the right posterior, right anterior, or left lateral lobes, away from portal and hepatic veins. Each measurement lasted 15 sec. We performed the measurement with both the standard STEAM sequence with five different acquisitions (five breath holds), each one corresponding to a different echo time, and the HISTO sequence (one breath hold) (figure 2). The TR, bandwidth, sampling points, signal accumulations and TE values were the same for both sequences. The parameters applied were optimized for the clinical application (TR/TM=3000/10 and TE=12, 24, 36, 48 and 72). The shimming was redone for each sequence.

2.4. Spectrum post-processing

We exported the spectra from the Siemens console to a personal computer and analyzed them with the software package jMRUI Version Number: 2.2, with the AMARES quantification [4]. The signal integrals of water (H_2O at 4.7 ppm) and lipids (CH_2 and CH_3 at 1.3 ppm and 0.95 ppm) were quantified for each echo time.

2.5. R2 calculation, lipid content estimation and correlation with iron content

With spectral integrals obtained at multiple TE's using HISTO, mono-exponential linear curve fittings were performed using the equation $S = S_0*\exp(-R2*TE)$ to estimate both R2 and S_0, for water and lipid signals. Subsequently, lipid content was calculated as: $\text{Lipid\%} = S_{0fat}/(S_{0fat}+S_{0water})*100$. Signal saturation from incomplete T1 relaxation is minimized using a long TR. In other studies, lipid content was measured by simply looking at fractional fat signal at a given TE. To demonstrate that such an approach is inaccurate, fat content was also calculated using the integrated signal at TE = 12 msec. To assess the ability to ascertain iron content based on the derived R2, the R2 of water measured by MRS was compared to the iron concentration using linear regression.

3. RESULTS

Table 1 lists the results of the estimated lipid content, with and without T2 correction, in the phantoms which had a known lipid content of 10% and 30%. Percent fat calculated with STEAM (TE = 12 ms) shows strong deviations as iron content increases, while HISTO with T2 correction remains relatively stable. The T2-corrected percentage of fat and R2 of water calculated in the patients are given in Table 2; the values obtained with both techniques are similar, suggesting equivalence between the two techniques for measuring the same unknown variables. In the phantoms, we observed a correlation between the R2 value of water and the amount of iron in the sample, independently of the fat percentage (figure 3). Regression analysis revealed a highly significant linear relationship: $R2 = 280.08 \times [Fe] + 14.599$ ($r= 0.9796$, $p = 0.0001$), with [Fe] in units of mM and R2 in sec^{-1}. The R2 standard error was 8.46 sec^{-1}. The intercept represents the average R2 of agarose without iron across the 3 different percentages of fat. The lipid content derived by using S_0 was accurate for all iron concentration levels following but differed in value from the estimate obtained without T2 correction. This trend was most significant for high iron concentrations (0.5mM).

4. DISCUSSION

Increased iron deposition occurs in many chronic liver diseases, Wesphalen et al [5] demonstrated that in 25 of 38 patients liver iron deposition was found and liver fat percentage was identified histopathologically in 14 of 38 and in nine of 25 patients with iron deposition. Opposed-phase MRI has been used in several studies to assess the lipid content in liver. For example, Chang et al [6] claimed an accurate estimation of fat fraction using opposed-phase imaging with qualitative ^{1}H MRS to resolve the ambiguity of fat or water dominance. However, signal loss on in-phase image caused by the presence of liver iron is a potential pitfall in the determination of liver fat percentage in opposed-phase MRI and MRS for chronic liver diseases. Machann et al [7] proposed the Fat-selective MRI technique for the assessment of the amount and spatial distribution of HL. In this study, Fat-selective MRI and ^{1}H-MRS were compared and led to very similar results, showing correlation coefficients of r = 0.95 or better. But unfortunately, in both techniques, the T2 effects were uncorrected for. For MRS under ideal imaging conditions, an estimation of lipid % can be measured by relating the magnitude of the two spectra. However, absolute magnitude of water and lipid spectra within a voxel can be modified by T2 effects in the presence of iron. The

estimation of lipid content, therefore, will depend highly on the TE of the MRS sequence. This causes a non-negligible T2 error in MRS lipid content measurements that must be corrected to achieve consistent and accurate results. MRS techniques proposed to assess the iron concentration require a long examination time. Wang et al [3] applied 12 echo times for the R2 estimation, ranging from 1.5 ms to 100 ms, with the number of signal averages varying from 20 for the shortest TE to 40 for the longest TE. The total time for the MRI and MRS acquisitions was around 25 minutes. The water and fat signals were each fitted by a mono-exponential decay function to estimate R2. The signals were acquired without respiratory gating or breath-holding. The authors tested the results with and without breath-holding in one healthy volunteer and the results were the same. These authors used an extended range of echo times to obtain a mono-exponential fit. Using HISTO, we distributed the five echo times from 12 ms to 72 ms. With these echoes, we had a sufficient number of points to perform an accurate mono-exponential fit, balancing the requirements of curve-fitting and of a clinically viable 15 s total acquisition that could be obtained in a single breath hold.

Another requirement of a clinically viable MRS method is to be easily implemented even in centers without extensive expertise in spectroscopy. The observed relative robustness of HISTO to imperfect shimming is another highly attractive feature of this method. This finding may be explained on the basis of proportional lipid/water signal determinations. Proportional broadening of these signals from imperfect shimming may therefore not alter their relative ratio, at least to the degree evaluated in our testing.

MRS is theoretically preferable to MRI, for detecting small variations in fat content in response to interventions or for disease monitoring. However, most of the MRS methods require several minutes of acquisition and post-processing and are therefore not amenable to broad application. In addition, these methods require breathing within the TR interval and to exhale in phase with each data acquisition or synchronize the acquisition to the breath of the patient in order to minimize line broadening [3,7]. Nevertheless, other physiological movements cannot be avoided. A fast acquisition method is needed in order to avoid all physiological movements but also intra-echo variations. The advantages of HISTO in comparison to the previously proposed methods are that, 1) it is a spectroscopic technique more sensitive than MRI for an accurate quantification and monitoring of changes in HL levels, 2) it does not require complex corrections for either T2 or T1 effects, as some MRI techniques do, 3) it allows the assessment of T2, and therefore estimation of the body iron content, by the acquisition of several echoes, 4) it corrects for the iron effects, an adjustment never performed before for hepatic lipid quantification, 5) it is a fast acquisition method (15 seconds) that does not require complicated data post-processing, in comparison to prior methods not amenable to broad application.

5. CONCLUSION

HISTO is an accurate and fast technique which allows, in 15 seconds, the acquisition of several echoes in order to assess the T2 of water and lipids and determine the corrected lipid concentration. Failure to correct for T2 variations will result in significant errors in lipid measurement. In this study, the feasibility and accuracy of HISTO in rapidly measuring lipid and iron concentrations simultaneously has been demonstrated experimentally in phantoms and patients with fatty liver disease.

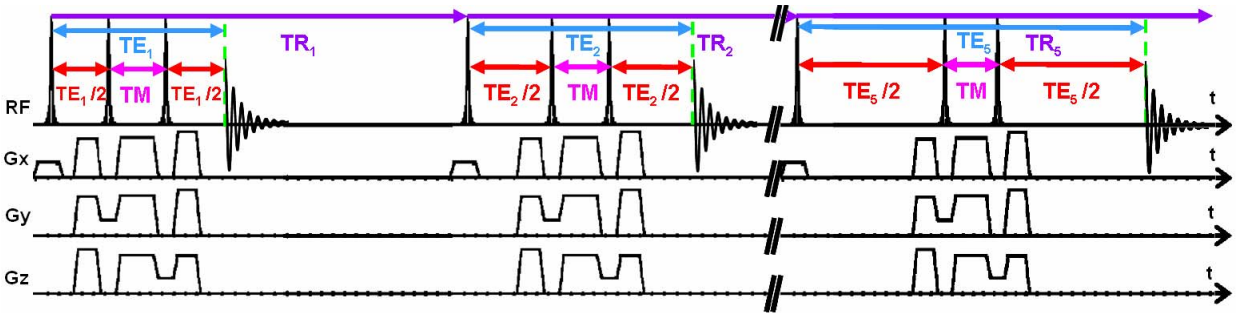

Figure 1:HISTO diagram based on the STEAM sequence. Repetition Time (TR: TR1=TR2 =…=TR5). Echo time (TE1<TE2<…<TE5), TM = Mixing time.

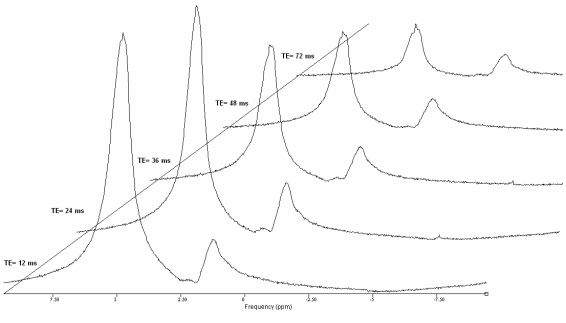

Figure 2: Five echo acquisition in a patient with fatty liver. TR= 3s, TE= 12, 24, 36, 48 and 72 msec. The amplitude of the peaks is reduced by the spin-spin relaxation (T2).

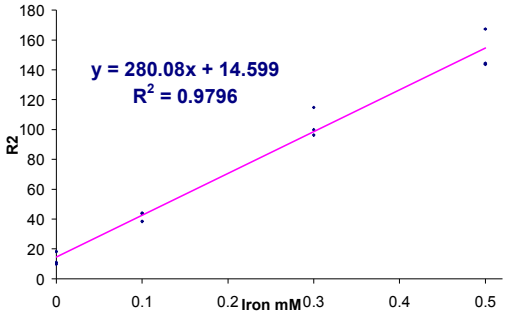

Figure 3: Linear regression of R2 (sec^{-1}) and iron concentration with different percentages of fat in phantoms.

Phantom	% fat T2 corrected	% fat TE = 12 ms
10% fat 0 mM iron	8.75	8.14
10% fat 0.1 mM iron	11.61	11.86
10% fat 0.3 mM iron	9.06	17.97
10% fat 0.5 mM iron	9.36	28.81
30% fat 0 mM iron	29.70	29.19
30% fat 0.1 mM iron	27.23	32.15
30% fat 0.3 mM iron	34.35	57.36
30% fat 0.5 mM iron	33.80	64.66

Table 1: Calculation of fat percentage in phantoms.

	Patient 1		Patient 2	
	STEAM	HISTO	STEAM	HISTO
R2 water	27.74	27.54	24.69	25.30
% fat T2 corrected	19.90	20.66	13.81	13.70

Table 2: Comparison between standard STEAM sequence and HISTO sequence. R2 values in patients are given in sec^{-1}.

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